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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/804,584	03/12/2001	Matthew L. Albert	600-1-276 CIP	5033

23565 7590 02/23/2005

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 02/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/804,584	ALBERT ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-41* is/are pending in the application.

4a) Of the above claim(s) *5-14,20 and 23-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 4, 15-19, 21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action..

Claims 1 and 21 have been amended. Claim 3 has been canceled. Claims 1, 2 and 4-41 are pending. Claims 23-41, drawn to non-elected inventions are withdrawn from consideration. Claims 5-14 and 20, drawn to non-elected species are also withdrawn from consideration. Claims 1, 2, 4, 15-19, 21 and 22 are under consideration.

The rejection of claims 1, 2, 4, 15-17, 19, 21, 22 under 35 U.S.C. 103(a) as being unpatentable over Albert et al (U.S. 2002/014396, priority to 09/251,896, filed February 19, 1999) in view of Kirberg et al (European Journal of Immunology, 1003, Vol. 23, pp. 1963-1967) and Migita et al (Journal of clinical Investigation, 1995, Vol. 96, pp. 727-732, cited in a previous Office action is maintained for reasons of record.

Claim 1 is drawn to a method for inducing tolerance in a mammal to an antigen comprising the steps of isolating peripheral blood mononuclear cells from said mammal; isolating dendritic cells from said peripheral blood mononuclear cells; exposing said dendritic cells ex vivo to apoptotic cells expressing said antigen in the presence of at least one dendritic cell maturation stimulatory molecule and in the absence of effective CD4+T cell help, wherein said dendritic cells upon exposure to said dendritic cell maturation stimulatory molecule are characterized as having the phenotype CD14- and CD83+ i; and introducing a cellular portion of step (c) into said mammal; wherein said dendritic cells induce apoptosis of antigen-specific CD8+ T cells in said mammal resulting in tolerance to said antigen. Claim 2 embodies the method of claim 1 wherein dendritic cell maturation molecule is selected from the group consisting of PGE2, TNF-alpha,Il-6, Il-1 beta, LPS, monocyte conditioned medium, CpG-DNA or any combination thereof. Claim 4 embodies the method if claim 1 wherein said absence of effective CD4+ T-cell help is achieved by including in step (c) at least one agent that inhibits or eliminates effective CD4+ T cell help. Claim 15 embodies the method of claim 4 wherein said agent inhibits signaling consequent to dendritic-cell CD4 T cell engagement. Claim 16 embodies the method of claim 15 wherein said agent is a FKBP antagonist. Claim 17 specifies that the

FKBP antagonist is FK506 (tacrolimus). Claim 19 embodies the method of claim 1 wherein said antigen is a viral antigen, a self antigen or a transplantation antigen. Claim 21 embodies the method of claim 1 wherein the infusion of the cellular portion of step (c) is done after the dendritic cells mature and exhibit the phenotype CD14- and CD83+ . Claim 22 embodies the method of claim 1 wherein said mammal is human.

Albert et al teach a method for using apoptotic cells to deliver antigen to dendritic cells for tolerization of T-cells (page 2, paragraphs [0024] and [0025]) Albert et al teach that the dendritic cells are obtainable by culturing PMBCs (page 7, paragraphs [0083-0085]) with a combination of Tl-4 and GM-CSF to promote the differentiation into immature, antigen-capturing dendritic cells (page 7, paragraph. [0086], lines 8-10). Albert et al teach that maturation of dendritic cells requires the presence of dendritic cell maturation factors which include LPS, PGE2, TNF-alpha, Il-6, Il-1 beta, monocyte conditioned medium or necrotic cells (page 7, paragraph [0086], lines 15-19 and pages 21-22, paragraph [0213], lines 13-17). Albert et al teach that the mature dendritic cells exhibit the phenotype of Cd14-, CD83+, and HLA-Drhi (page 18, table).

Albert et al teach that phagocytosis of apoptotic cells versus necrotic cells failed to mature the dendritic cells (page 22, paragraph [0215], lines 9-13). Albert et al teach that dendritic cells exposed to a mixture of apoptotic cells and necrotic cells induced similar increases in T-cell stimulation as dendritic cells cultured with necrotic cells and that dendritic cells exposed in parallel to apoptotic cells and monocyte conditioned medium heightened T-cell responses to the same extent as dendritic cells matured with monocyte conditioned medium, both experiments indicating that ingestion of apoptotic cells did not inhibit maturation or function of the dendritic cells (page 22, paragraph [0217], lines 22-30). Albert et al teach that phagocytosis of apoptotic cells may lead to T-cell immunity if followed by a maturation signal and that signals provided by the necrotic cells such as TNF-alpha, Il-1 beta and IFN-gamma, inflammatory products such as LPS and CD+4 T-cells would be required for the full activation of T-cells (page 23, lines 1-13). Albert et al cite publications which teach that model systems of cross-priming and cross tolerance indicate that induction of CTL requires CD+4 help (page 23, last sentence). Albert et al do not specifically teach the induction of tolerance comprising the maturing of dendritic cells in the absence of CD+4 help.

Kirberg et al teach that CD+4 T-cell help prevents the rapid deletion of CD+8 T-cells after a transient response to antigen.

Migita et al teach that FK506 exclusively induced apoptosis of antigen-stimulated T-cells (page 731, first column, lines 11-16 of the first full paragraph, and second column, first paragraph).

It would have been prima facie obvious at the time the claimed invention was made to expose immature dendritic cells ex vivo to apoptotic cells in the presence of dendritic cell maturation factors of PGE2, TNF-alpha, Il-6, Il-1-beta, LPS or monocyte conditioned medium and introduce said matured dendritic cells into a mammal in the presence of FK506. One of skill in the art would be motivated to do so by the teachings of Albert et al on the maturation of dendritic cells exposed to apoptotic cells by dendritic cell maturation factors, and the suggestion of Albert et al that the presence of CD+4 T-cell help is necessary for the full activation of T-cells and the teachings of Kirberg et al on the rapid deletion of CD+8 T cells after transient response to antigen when the T-cell encounters said antigen in the absence of CD+4 T cell help. One of skill in the art would under stand that the administration of the matured dendritic cells exposed to apoptotic cells and the maturation stimulatory factors would be potent antigen-presenting cells and cause activation of CD+8 T-cells specific for the antigens derived from the apoptotic cells. One of skill in the art would understand by the teachings of Kirberg et al that the specific CD+8 T-cells would be eliminated apoptotically after this transient activation in the absence of effective CD+4 T-cell help. One of skill in the art would recognize that FK506 would induce apoptosis of antigen-stimulated T-cells which include CD+4 T-cells and would be effective at eliminating CD+4 T-cell help.

Claims 1, 2, 4, 15-19, 21 and 22 under 35 U.S.C. 103(a) as being unpatentable over Albert et al (U.S. 2002/014396, priority to 09/251,896, filed February 19, 1999) and Kirberg et al (European Journal of Immunology, 1003, Vol. 23, pp. 1963-1967) and Matzinger (Annual Review of Immunology, 1994, Vol. 12, pp. 991-1045) and Migita et al (Journal of clinical Investigation, 1995, Vol. 96, pp. 727-732, cited in a previous Office action)as applied to claims 1, 2, 4, 15-17,

19, 21 and 22 above, and further in view of Li et al (Transplantation, 1998, Vol. 66, pp. 1387-1388) and Sehgal (Clinical biochemistry, 1998, Vol. 31, pp. 335-340).

Claim 18 embodies the method of claim 16 wherein said TOR antagonist is rapamycin. The combination of Albert et al and Kirberg et al and Matzinger and Migita et al render obvious claims 1, 2, 4, 15-17, 19, 21 and 22 with respect to the administration of FK506 as an agent which eliminates effective CD+4 T-cell help by means of inhibiting dendritic-cell Cd+4 T-cell signaling consequent to dendritic cell CD+4 T-cell engagement. None of the references teach rapamycin as an agent which eliminates dendritic-cell Cd+4 T-cell signaling consequent to dendritic cell CD+4 T-cell engagement.

Li et al teach that CTLA4Ig combined with rapamycin results in a permanent tolerization to a tissue engraftment. Li et al teach that rapamycin blocks Il-2 induced proliferative but not apoptotic signals required to achieve tolerance to an antigen (page 1387, second column, second full paragraph). Sehgal teaches that rapamycin complexes with the immunophilin FKBP to produce the mammalian inhibitor of rapamycin complex which blocks the Il-2 mediated signal transduction pathway that prevents cell cycle progression from G1 to S-phase in T-cells (page 336, second column, lines 4-9).

It would have been prima facie obvious at the time the claimed invention was made to substitute rapamycin for FK506 in the method rendered obvious by the combination of Albert et al and Kirberg et al and Migita et al. One of skill in the art would have been motivated to do so by the teachings of Li et al on the blockage of Il-2-idnuced proliferative signals by rapamycin and the teachings of Sehgal et al that rapamycin blocks the Il-2 signal transduction pathway that prevents T-cells from entering the S-phase and thus proliferating. One of skill in the art would recognize from the teachings of Sehgal et al that rapamycin would prevent the proliferation of activated T-cells which include CD+4 T cells; one of skill in the art would recognize from the teachings of Li et al that rapamycin would not inhibit an Il-2 induce apoptotic signal and thus not block the apoptosis of antigen-stimulated CD+4 T-cells or CD+8 T cells.

Applicant argues that the Ablert reference does not constitute proper prior art because it was published after the effective priority date of the instant application. Applicant quotes the amendment of May 27, 2003, wherein an amendment to the specification was made stating that

09/251, 896 claims priority to 60/075, 356, filed February 20, 1998; 60/077, 095, filed March 6, 1998 and 60/101746, filed September 24, 1998. This has been considered but not fond persuasive. Applicant's attention is drawn to the Office action mailed March 1, 2004 wherein it is stated on page 2 that

Acknowledgement is made of applicants claim to the priority documents of 60/075,356, filed February 20, 1998, 60/077,095, filed March 6, 1998 and 60/101,749, filed September 24, 1998. After review and reconsideration of these provisional application it is concluded that they do not provide adequate written description for the instant invention. 60/075,356 and 60/077,095, although providing a written description of cross presentation of antigens via dendritic cells which are exposed to apoptotic cells having said antigen, makes o reference to a method of inducing tolerance to said antigen by exposing the dendritic cells to apoptotic cells without helper T-cells. 60/101,749 briefly ,mentions that tolerance can be induced by exposing dendritic cells to apoptotic cells in the absence of T helper cells as in the method of Steinman (Immunol Rev 1997, Vol. 156, pp. 25-37). Upon consulting the cited paper it is noted that Steinman contemplates a specialized resident population of dendritic cells within the T-cell areas that express high levels of self-antigen and functional fas ligands capable of inducing CD+4 T cell death (abstract). Stenman speculates that "a lack of CD+4 helper T cells may in turn be pivotal for maintaining the silence of those self-reactive B cells and CD8= killer cells that escape central deletion in the marrow or the thymus". However, none of the provisional applications provide adequate written description of a method wherein T-cell help is eliminated by methods other than the simple exclusion of T-helper cells from the dendritic cells in the presence of the apoptosis cells. Accordingly, the instant invention will be given the priority date of the 09/565, 958 application, May 5, 2000.

Therefore the Albert et al reference is a proper prior art reference.

Applicant again argues that Albert et al does not teach or suggest that the absence of CD+4 T-cell help, or the inhibition of CD+4 T-cell help consequent to dendritic cell CD+4 T-cell engagement is a requirement in conjunction with the generation of CD14-, CD83+ dendritic cells following the addition of maturation factors. Applicant is reminded that the rejection was made under 35 U.S.C. 103(a). Albert et al was not relied upon for the total teachings of the instant method.

Applicant argues against the references in a piecemeal fashion indication as a whole what each reference teaches. This has been considered but not found persuasive. As stated in the previous Office action, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues that it was not until Applicant's present invention that the precise steps involved in tolerance induction by presenting antigen to dendritic cells via apoptotic cells in the presence of dendritic cell maturation factors but in the absence of T-cell help resulted in the generation of dendritic cells bearing the phenotype of CD14- and CD83+, which upon transfer to a subject resulted in the apoptosis of antigen-specific T-cells. This has been considered but not found persuasive. Alberts et al teach the antigen to dendritic cells via apoptotic cells in the presence of dendritic cell maturation factors causing the maturation of dendritic cells expressing the phenotype of CD14- and CD83+. The abstract of Kirberg et al teaches that the presence of CD+4 T-cell help prevents the rapid deletion of CD+8 T-cells after an initial transient response to antigen. One of skill in the art would reasonable conclude that the absence of CD+4 help results in the rapid deletion of CD+8 T-cells after an initial transient response to antigen. Matzinger teaches that CTL become unresponsive to their antigen if said CTL encounter said antigen in the absence of CD+4 T-cell help. One of skill in the art would understand that T-cells encounter the matured dendritic cell presenting the antigen(s) of the apoptotic cells would result in the formation of CD+8 T-cells which would be tolerized to antigen, rather than activated, if CD+4 T-cell help was eliminated, because both the abstract of Kirberg et al and Matzinger teaches that CD+4 T-cell help is necessary for the maintenance of CD+8 T-cells after the first encounter with their antigen.

The amendment filed on May 27, 2003 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The amendment bodily incorporated 60/075, 356, filed February 20, 1998; 60/077, 095, filed March 6, 1998 and 60/101746, filed September 24, 1998 by reference, which constitutes new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
2/22/2005

KAREN A. CANELLA PH.D
PRIMARY EXAMINER